AlzPED: An Open Science Tool Raising the Standards for Preclinical Testing of Candidate Therapeutics in Alzheimer's Disease Animal Models.

Jaya Viswanathan, PhD
Program Analyst, AlzPED team,
Translational Research Branch, Division of Neuroscience
Email: jaya.viswanathan@nih.gov

National Institute on Aging

SOCIETY FOR NEUROSCIENCE INTERNATIONAL CONFERENCE

Nanosymposium: NANO63
Therapeutic Strategies: Animal Models
November 14, 2023

Preclinical to Clinical Translation Gap

Symptomatic Full Approval	Disease Modifying Monoclonal Antibody Accelerated/ Full Approval
Donepezil (Aricept) 1996	**Aducanamab** (Aduhelm) Anti-amyloid; 2021 Accelerated approval
Rivistagimine (Exelon) 2000	**Lecanemab** (Leqembi) Anti-amyloid; 2023 Full approval
Galantamine (Razadyne) 2001	
Memantine (Namenda) 2003	
Donepezil and Memantine (Namzaric) 2014	

- **More than 200 therapeutic agents have been reported to be efficacious in ameliorating pathology and/or cognitive deficits in transgenic AD animal models.**
- **High rate of attrition of AD drug candidates in Phase II (92%) and Phase III (98%) with more than half failing due to lack of efficacy.**
- **Till date, only 7 drugs have received FDA approval as therapies for patients in the clinic.**

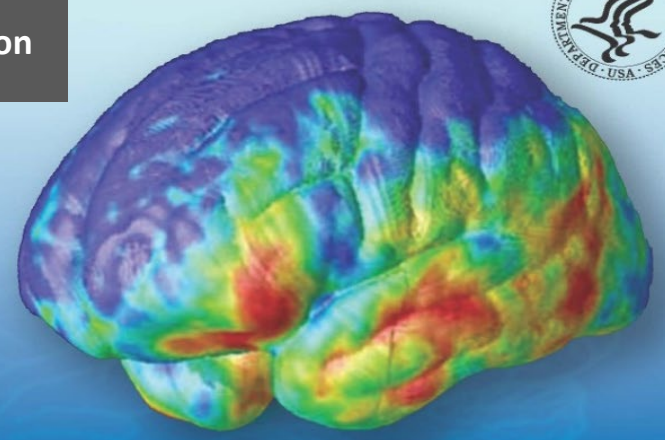
Zahs & Ashe, Trends in Neurosciences, 2010
Cummings et al., Alzheimer's Research & Therapy 2014
Cummings, Drugs 2023

Factors Contributing to Poor Translation of Preclinical Efficacy Testing

- The AD animal models do not accurately recapitulate human AD.
- Lack of reliable preclinical biomarkers that translate to the clinic.
- Failure to match outcome measures used in clinical studies.
- Lack of standardization and rigor in study design and analysis of data.
- Poor reproducibility of published data.
- Publication bias due to under reporting of negative results in the literature.

Shineman et. al., Alzheimer's Research &Therapy, 2011

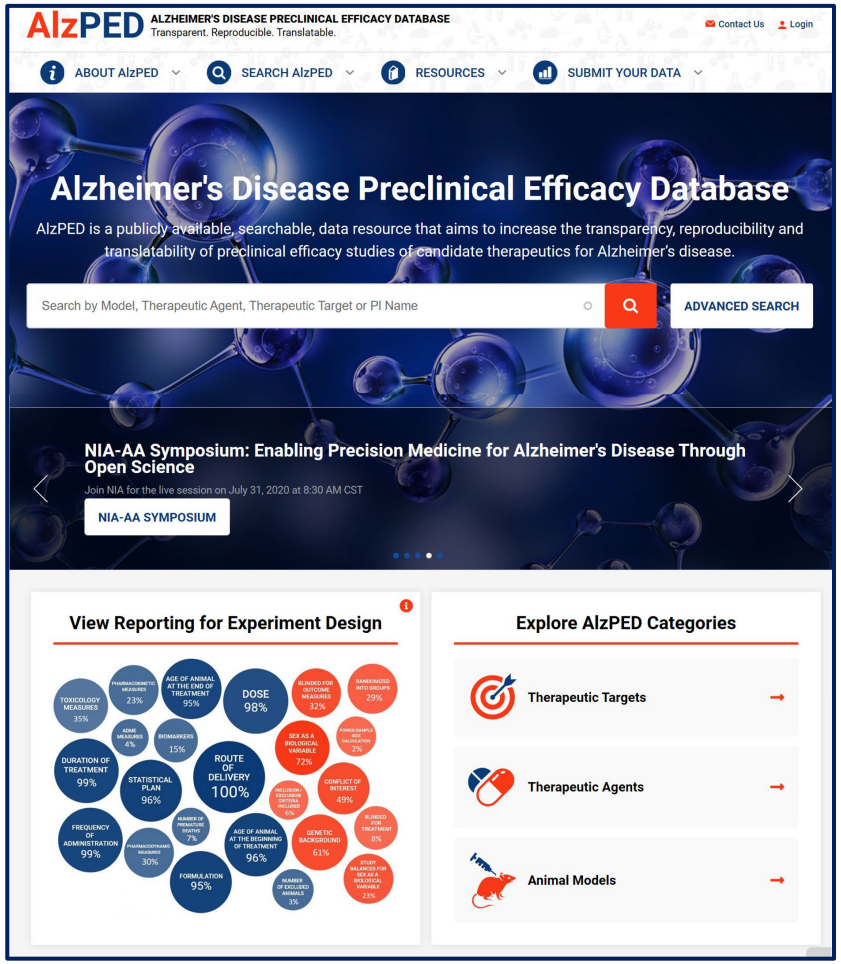
NIH AD Research Summits:
Path to Treatment and Prevention



May 14-15, 2012
Feb 9-10, 2015
March 1-2, 2018
April 19-22, 2021

1. House experimental details relating to the preclinical testing of candidate therapeutic agents in AD animal models.
2. Identify critical elements of design and methodology missing from studies.
3. House experimental details of positive and negative data to overcome publication bias.

NIH AD Summits :
Recommendations Aimed at Increasing the Predictive Validity of Preclinical Studies in AD Animal Models



https://alzped.nia.nih.gov

Recommendations: Best Practices and Study Guidelines for Preclinical Animal Studies

- Power Analysis/Sample Size
- Statistical Analysis Plan
- Inclusion/Exclusion Criteria
- Randomization
- Blinding (treatment allocation and outcome measures)
- Balance for Gender
- Report Age of Animals
- Report details of Strain, Housing, Diet
- Employ *translatable biomarkers* as key measures
- Use PK/PD, ADME to Characterize Candidate Therapeutic Agents
- Report Toxicology Measures
- Report Potential Conflicts of Interest
- **Develop a Publicly Available Database of Preclinical Efficacy Studies (Similar to Clinical Trials.gov.)**

Common Critical Elements of Clinical Trial Study Design

van der Worp et al PLoS, 2010

AlzPED: Scope and Capabilities

- Growing database, currently hosts curated summaries of 1400 preclinical therapeutic studies in AD animal models published between 2000 and 2022.
  - Provides the research community with an easy way to survey existing AD preclinical therapy development literature with access to information on study design and methodology, animal models, therapeutic agents, therapeutic targets, outcomes, patents and related clinical trials.

- Designed to monitor the scientific rigor of curated studies with a "Rigor Report Card" consisting of a standardized set of 24 experimental design elements recommended by expert advisory groups during the 2015 NIH AD Summit.
  - Reports on the rigor of each curated study by summarizing the elements of experimental design and identifying critical elements of experimental design missing from the study.

- Provides a platform for creating citable reports of unpublished studies, including studies with negative findings.
  - Mitigates publication bias due to under-reporting of negative results in the literature.

- Provides funding agencies with a tool for enforcement of requirements for transparent reporting and rigorous study design.

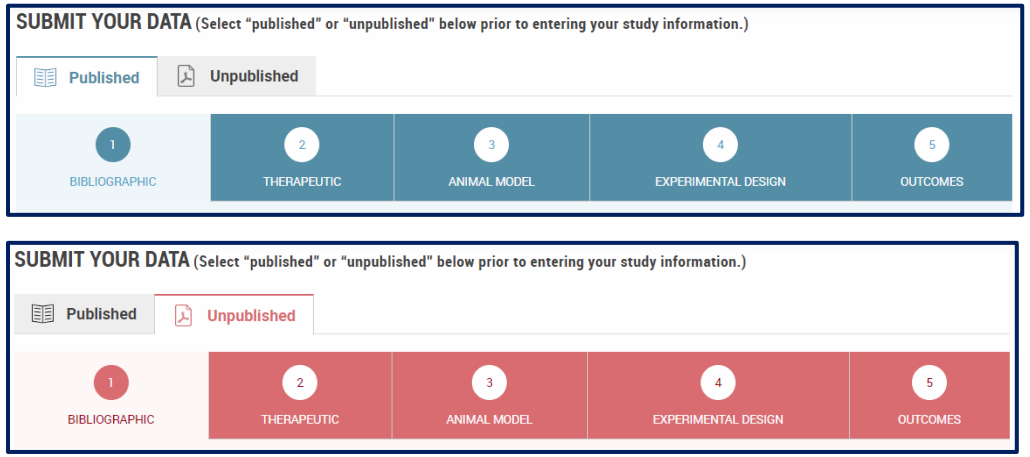
- Provides search capability across relevant translational criteria data sets and external databases:

  - Therapy Type (16 Therapy Types)
  - Therapeutic Agent (1201 Therapeutic Agents)
  - Therapeutic Target (274 Therapeutic Targets)
  - Animal Model (226 Animal Models)
  - Principal Investigator
  - Funding Source

  - Related Publications (PubMed)
  - Therapeutic Agents (PubChem and Drug Bank)
  - Therapeutic Targets (Open Targets, Pharos and Agora)
  - Animal Model (Alzforum)
  - Related Clinical Trials (ClinicalTrials.gov)
  - Related Patents (Google Patents and USPTO)

Article Selection and Curation Workflow

AlzPED Data Submission Portal:



Article Selection:

- **Published studies** are collected from databases like PubMed and Embase using key word search strings specific to preclinical therapeutic testing in AD animal models.
- **Unpublished studies** (including negative data) are obtained directly from researchers.

Curation Workflow:

Submitted study reviewed and curated by 2 NIA experts in AD research for

- Bibliographic details, funding source, study goals
- Therapeutics – therapy type, therapeutic agent and target
- Animal model
- Scientific rigor and experimental design (using Rigor Report Card)
- AD-related outcome measures

↓

Curated summary is hosted on AlzPED

Sample of a Curated Record on AlzPED

Prophylactic evaluation of verubecestat on disease and symptom modifying effects in 5XFAD mice

Unpublished

BIBLIOGRAPHIC | THERAPEUTIC AGENT | ANIMAL MODEL | EXPERIMENTAL DESIGN | OUTCOMES

Bibliographic

Year of Publication: 2021

Contact PI Name: Stacey J. Sukoff Rizzo

Contact PI Affiliation:
University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Co-Authors:
AL Oblak, ZA Cope, SK Quinney, R Pandey, C Biesdorf, AR Masters, KD Onos, L Haynes, KJ Keezer, JA Meyer, J Peters, SC Persohn, AA Bedwell, K Eldridge, R Speedy, G Little, S-P Williams, M Sasner, G Howell, G Carter, H Williams, BT Lamb, PR Territo

Primary Reference (DOI): 10.7303/syn26560918

Conflict of Interest:
Dr. Lamb has served as a consultant for AvroBio and Eli-Lilly

Study Goal and Principal Findings (Abstract):
Alzheimer's disease (AD) is the most common form of dementia. Beta-secretase (BACE) inhibitors have been proposed as potential therapeutic interventions however initiating treatment once disease has significantly progressed has failed to effectively stop or treat disease. Whether BACE inhibition may have efficacy when administered prophylactically in the early stages of AD has been under-investigated. The present studies aimed to evaluate prophylactic treatment of the BACE inhibitor verubecestat in an AD mouse model using the NIA resources of the MODEL-AD Preclinical Testing Core (PTC) Drug Screening Pipeline. 5XFAD mice were administered verubecestat ad libitum in chow from 3-6 months of age, prior to the onset of significant disease pathology. Following treatment, in vivo imaging was conducted with 18F-AV45 and 18-FDG-PET/MRI, brain and plasma beta-amyloid (Aβ) were measured, and the clinical and behavioral characteristics of the mice were assessed and correlated with pharmacokinetic data. Prophylactic verubecestat treatment resulted in dose- and region-dependent attenuations of 18F-AV45 uptake in male and female 5XFAD mice. Plasma Aβ40 and Aβ42 were also dose-dependently attenuated with treatment. Across the dose range evaluated, side effects including coat color changes and motor alterations were reported, in the absence of cognitive improvement or changes in 18F-FDG uptake. Prophylactic treatment with verubecestat resulted in attenuated amyloid plaque deposition when treatment was initiated prior to significant pathology in 5XFAD mice. At the same dose range effective at attenuating Aβ levels, verubecestat produced side-effects in the absence of improvements in cognitive function. Taken together these data demonstrate the rigorous translational approaches of the MODEL-AD PTC for interrogating potential therapeutics and provide insight into the limitations of verubecestat as a prophylactic intervention for early-stage AD.

Funding Source:
National Institutes of Health (NIH)
National Institute on Aging (NIA)

Experimental Design

Is the following information reported in the study?:

✓ Power/Sample Size Calculation	✓ Randomized into Groups
✓ Blinded for Treatment	✓ Blinded for Outcome Measures
✓ Pharmacokinetic Measures	✓ Pharmacodynamic Measures
✓ Toxicology Measures	✗ ADME Measures
✓ Biomarkers	✓ Dose
✓ Formulation	✓ Route of Delivery
✓ Duration of Treatment	✓ Frequency of Administration
✓ Age of Animal at the Beginning of Treatment	✓ Age of Animal at the End of Treatment
✓ Sex as a Biological Variable	✓ Study Balanced for Sex as a Biological Variable
✓ Number of Premature Deaths	✓ Number of Excluded Animals
✓ Statistical Plan	✓ Genetic Background
✓ Inclusion/Exclusion Criteria Included	✓ Conflict of Interest

Therapeutic Agent

Therapeutic Information:

Therapy Type: Small Molecule

Therapeutic Agent: Verubecestat

PubMed | PubChem | DrugBank | ClinicalTrials | Patents

Therapeutic Target: BACE1

Open Targets | Pharos | Agora

Animal Model

Model Information:

Species: Mouse

Model Type: APPxPS1

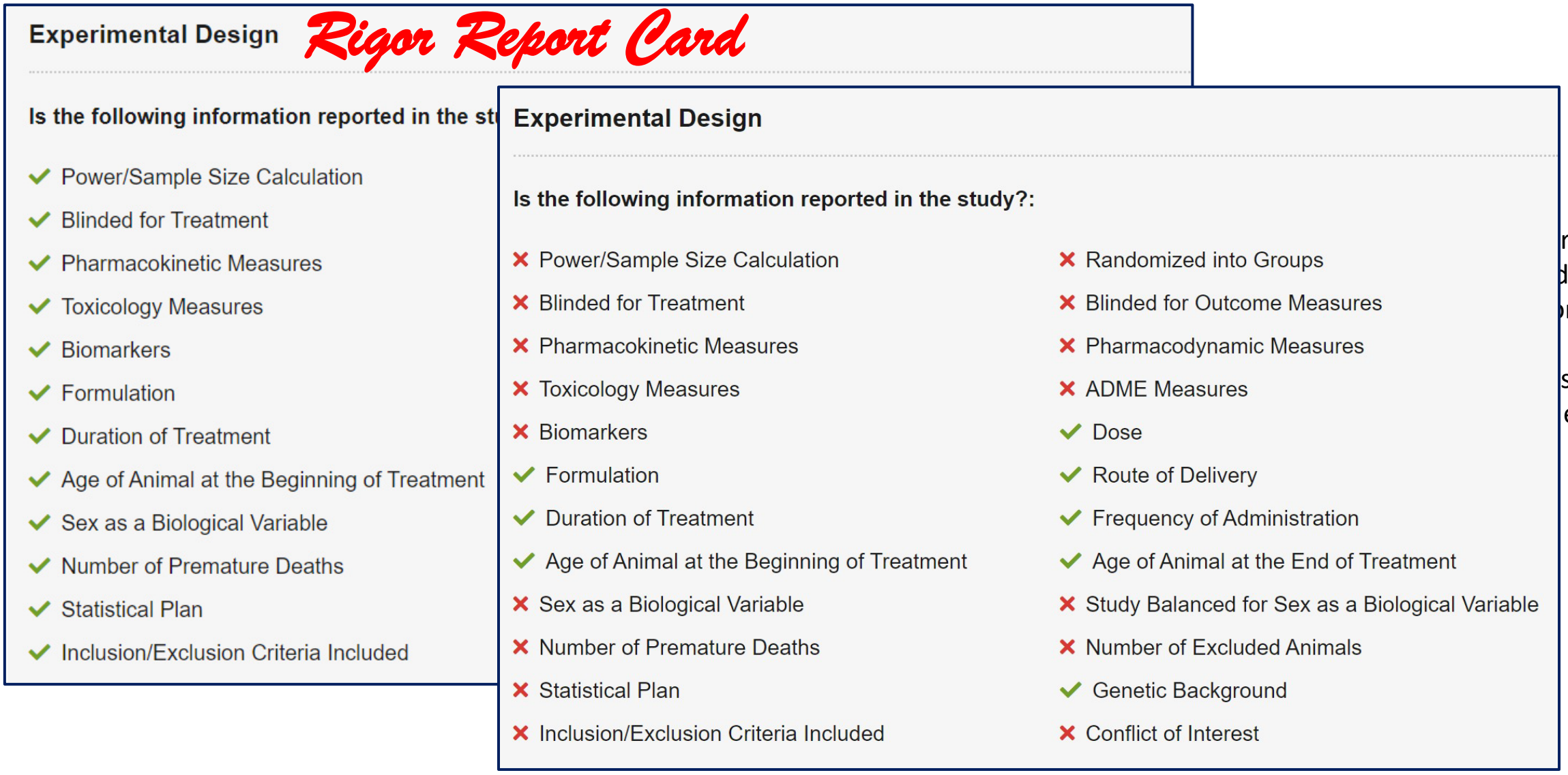
Model Name: 5xFAD ALZFORUM

Strain/Genetic Background: C57BL/6J

Outcomes

Outcome Measured	Outcome Parameters
Behavioral	• Exploratory Activity • Frailty Index • Open Field Test • Spontaneous Alternation
Motor Function	• Locomotor Activity • Path Length • Rotarod Test • Thigmotaxis
Histopathology	• Activated Microglia • beta Amyloid Deposits
Biochemical	• Brain-Buffer Soluble beta Amyloid Peptide 40 • Brain-Buffer Soluble beta Amyloid Peptide 42 • Brain-Formic Acid Soluble beta Amyloid Peptide 40 • Brain-Formic Acid Soluble beta Amyloid Peptide 42
Immunochemistry	• Ionized Calcium Binding Adaptor Molecule 1 (Iba1)
Spectroscopy	• Mass Spectrometry
Imaging	• [18F]AV45-PET • [18F]FDG-PET • Magnetic Resonance Imaging (MRI) • Standardized Uptake Value Ratio (SUVR)
Biomarker	• Plasma-beta Amyloid Peptide 42 • Plasma-beta Amyloid Peptide 40
Pharmacokinetics	• Brain/Plasma Ratio • Clearance (L/h/kg) • Cmax • Drug Concentration-Plasma • Drug Concentration-Brain • PK/PD Modeling • t1/2 (Elimination Half-Life) • Tmax • Volume of Distribution (V)
Pharmacodynamics	• Target Engagement (Reduction beta Amyloid Peptide 40-Brain) • Target Engagement (Reduction beta Amyloid Peptide 42-Brain) • Target Engagement (Reduction beta Amyloid Peptide 40-Plasma) • Target Engagement (Reduction beta Amyloid Peptide 42-Plasma)
Toxicology	• Body Weight • Coat Color Change • General Behavior • Physical Appearance
Omics	• Gene Expression Profile-Alzheimer's-Related Genes

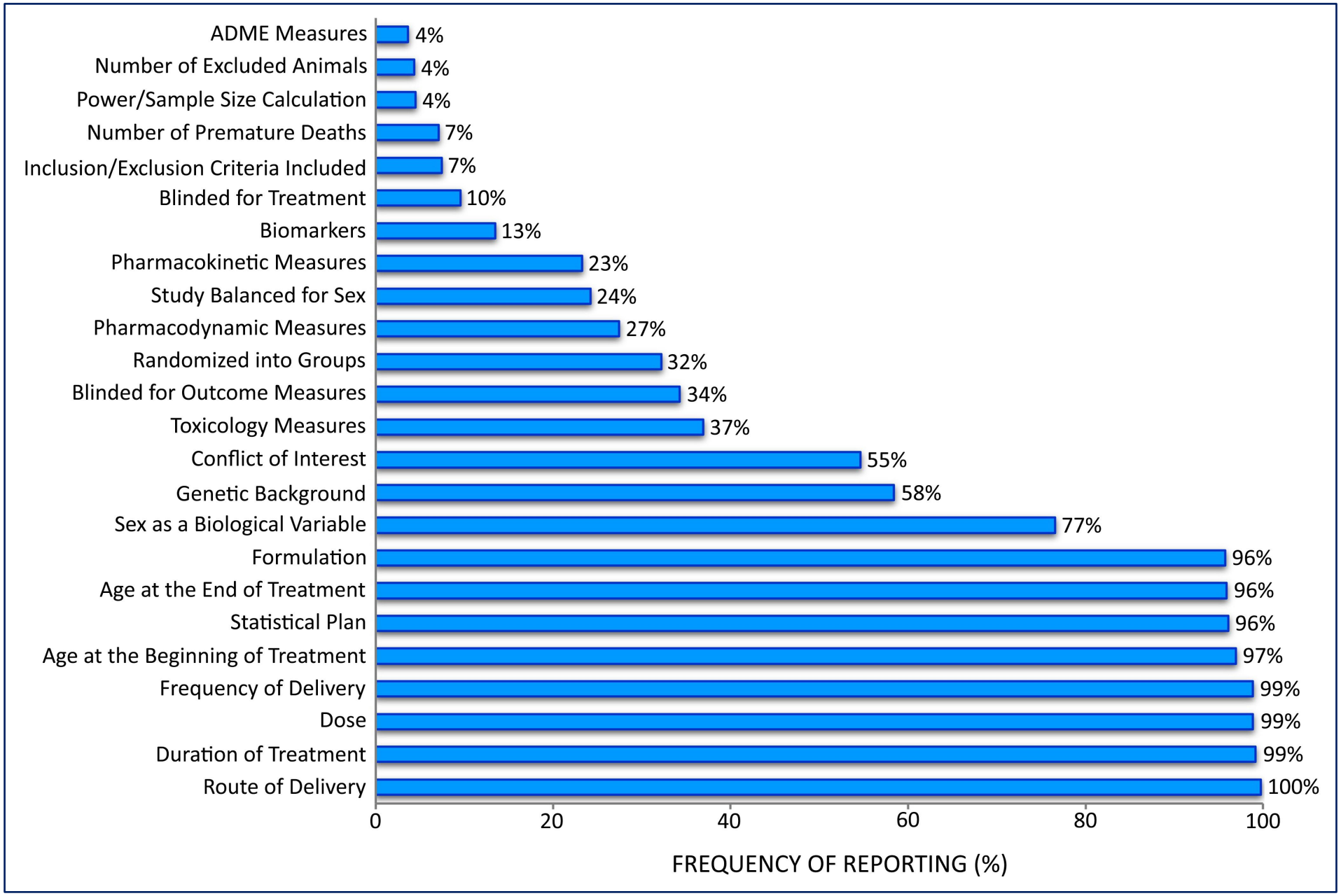
AlzPED Monitors Rigor in Study Design for Each Curated Study



r the
dies
nsisting

s
efficacy

Critical Elements of Experimental Design are Under-Reported

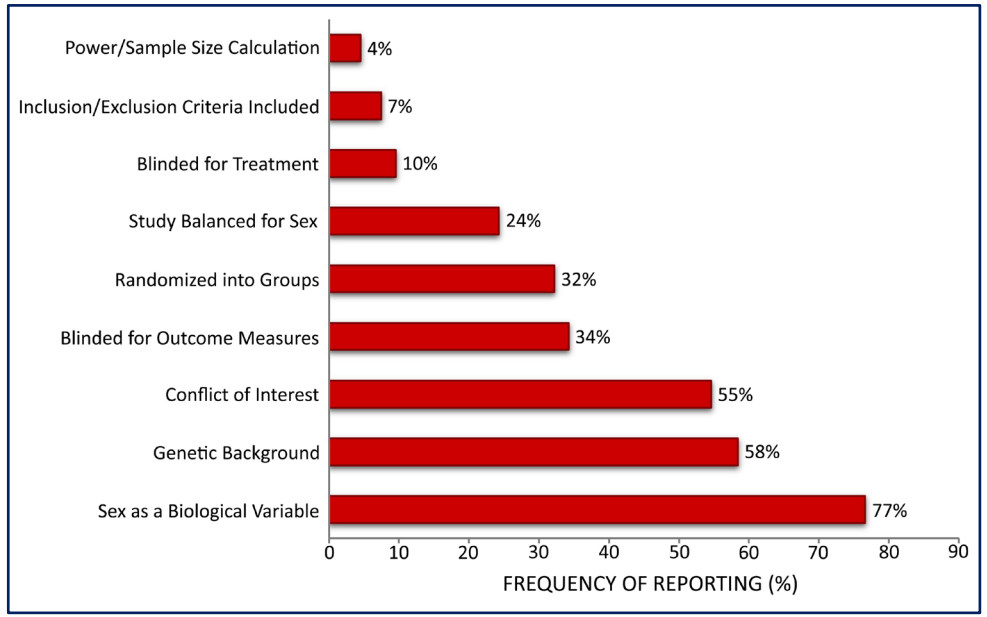


Graph shows the percentage of studies reporting the standardized set of 24 experimental design elements, calculated from 1400 published preclinical studies curated to AlzPED.

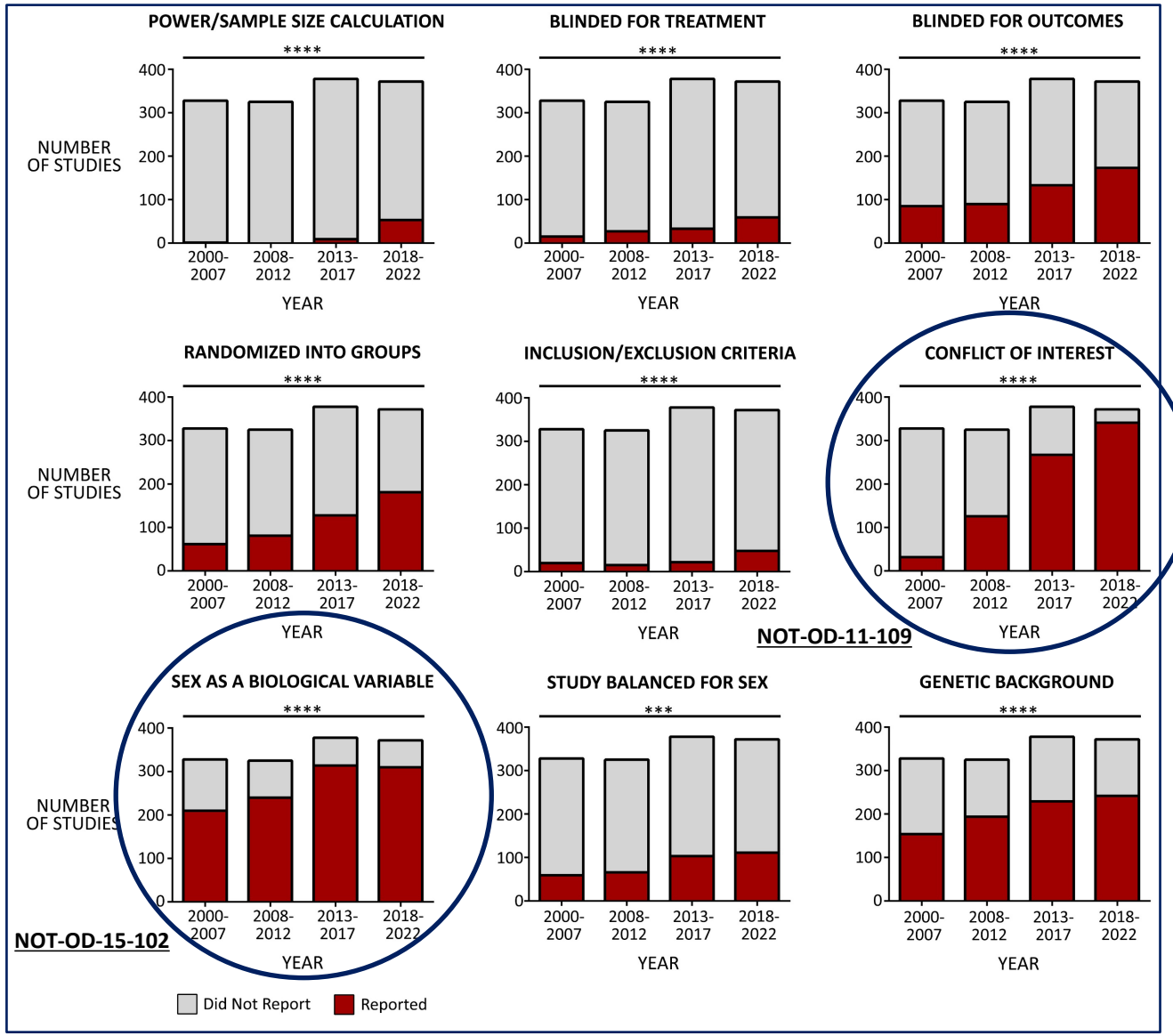
Detailed Analytics Summary is available on the AlzPED Analytics page.

Reporting Trends In The 9 Core Design Elements

9 core design elements are derived from Shineman et al., 2011, Landis et al., 2012, Snyder et al., 2016 and ARRIVE guidelines.



Graphs show reporting trends for the 9 critical core experimental design elements evaluated over 5-year spans from 2000 to 2022. Data analyzed using Chi square test; ***p<0.001, ****p<0.0001. Data presented as number that reported Vs number that did not report core experimental design elements, calculated from 328, 325, 378 and 372 curated studies published between 2000-2007, 2008-2012, 2013-2017 and 2018-2022 respectively.



Role of NIH Policies in Improving Rigor – evidence from reporting trends over 20 years from the AlzPED Database

NOT-OD-11-109 requires transparency in reporting financial conflicts of interest, and

NOT-OD-15-102 requires consideration of sex as a biological variable.

Enforcement of these policies clearly improved the reporting of these core experimental design elements.

NIA Funding Opportunity: *Integrative Research to Understand the Impact of Sex Differences on the Molecular Determinants of AD Risk and Responsiveness to Treatment (U01)* PAR-23-082

All findings from preclinical efficacy studies, including both negative and positive findings, are expected to be incorporated in AlzPED no later than 9 months after study completion or at the time of first manuscript publication, whichever comes first.

Published studies will be incorporated in AlzPED as a curated record; unpublished studies will be incorporated in AlzPED as a citable pre-print.

Training on conducting preclinical efficacy studies using mouse models of AD – Jax workshop

Principles and Techniques for Improving Preclinical to Clinical Translation in Alzheimer's Disease Research

MAY 6-10, 2024

An immersion workshop focusing on the improvement of preclinical translation in Alzheimer's Disease research. This workshop will leverage the expertise and facilities of the Indiana University (IU)/JAX Model Organism Development for Evaluation of Late Onset Alzheimer's Disease (MODEL-AD) Precision Medicine consortium.

https://www.jax.org/education-and-learning/course-and-conferences/principles-and-techniques-of-alzheimers-disease

Who Can Benefit from AlzPED

Academic and Industry Researchers

Leverage the AlzPED data to inform the design of your efficacy testing studies. Create citable reports of your (old and new) unpublished work including studies with negative findings.

Data Scientists

Use the multifaceted data to conduct a variety of meta-analyses and generate new insights on disease targets and candidate therapeutics.

Funding Agencies

Use AlzPED to assess the quality of the research you support and as a tool to enforce requirements for transparent reporting and rigorous study design.

Register for a free account:

https://alzped.nia.nih.gov/user/register

Submit your unpublished studies and get a citable preprint with a DOI

alzped@nih.gov

Acknowledgements

NIA

Shreaya Chakroborty
Maria Fe Lanfranco Gallofre
Zane Martin
Suzana Petanceska
Lorenzo Refolo
Erika Tarver
Jaya Viswanathan

Partner Organizations

NIH National Institute on Aging
NIH Library nihlibrary.nih.gov
Alzheimer's Drug Discovery Foundation
SageBionetworks
Cohen Veterans Bioscience
alz.org® | alzheimer's association®
BrightFocus® Foundation
Cure in Mind. Cure in Sight.

Disclosures

Nothing To Disclose

Rigor-related Resources

- **AlzPED Resources:** https://alzped.nia.nih.gov/resources
- **AlzPED and NIA Translational Research Blogs:** https://alzped.nia.nih.gov/blogs-and-presentations
- **AlzPED LinkedIn** – we post every few weeks with AlzPED, conference/workshop, and other NIA rigor and policy-related updates: https://www.linkedin.com/in/alzheimer%E2%80%99s-disease-preclinical-efficacy-database-alzped-13631a177/

- **NIH Advisory Committee to the Director Working Group on Enhancing Rigor, Transparency, and Translatability in Animal Research:** https://acd.od.nih.gov/working-groups/eprar.html
- **NIH Principles and Guidelines for Reporting Preclinical Research:** https://www.nih.gov/research-training/rigor-reproducibility/principles-guidelines-reporting-preclinical-research
- **NIH Resources for Preparing Your Application:** https://grants.nih.gov/policy/reproducibility/resources.htm
- **NIH Rigor and Reproducibility Training Modules:** https://grants.nih.gov/reproducibility/module_1/presentation_html5.html

- **ARRIVE Guidelines:** https://arriveguidelines.org/
- **ARRIVE Guidelines 2.0:** https://arriveguidelines.org/arrive-guidelines

- **National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs):** https://www.nc3rs.org.uk/
- **Global Preclinical Data Forum:** https://www.preclinicaldataforum.org/

NIA Translational Research Resources

- **International Alzheimer's and Related Dementias Research Portfolio (IADRP)** – database brings together funded research supported by public and private organizations both in the US and abroad all categorized using the Common Alzheimer's and Related Dementias Research Ontology (CADRO): https://iadrp.nia.nih.gov/
- **AD+ADRD Research Implementation Milestones:** https://www.nia.nih.gov/research/milestones
- **2021 NIH Alzheimer's Research Summit: Path to Precision Medicine for Treatment and Prevention:** https://www.nia.nih.gov/2021-alzheimers-summit
- **Alzheimer's Disease and Related Dementias Funding Opportunities:** https://www.nia.nih.gov/research/grants-funding/announcements
- **Accelerating Medicines Partnership® Program for Alzheimer's Disease (AMP® AD):** https://www.nia.nih.gov/research/amp-ad
- **AD Knowledge Portal:** https://adknowledgeportal.synapse.org/#/
- **Agora:** https://agora.adknowledgeportal.org/genes
- **Model Organism Development & Evaluation for Late-Onset Alzheimer's Disease (MODEL-AD):** https://www.model-ad.org/
- **Target Enablement to Accelerate Therapy Development for AD (TREAT-AD):** https://treatad.org/
- **Screening the Optimal Pharmaceutical for Alzheimer's Disease (STOP-AD):** https://stopadportal.synapse.org/#/
- **NIH Reporter:** https://reporter.nih.gov/
- Inside NIA – A Blog for Researchers: https://www.nia.nih.gov/research/blog
- **NIA and the National Plan to Address Alzheimer's Disease:** https://www.nia.nih.gov/about/nia-and-national-plan-address-alzheimers-disease